Please replace the paragraph at page 4, lines 1-12 with the paragraph rewritten as follows:

IL-17 has been shown to be produced by primary peripheral blood CD4+ T-cells upon stimulation, but was not detected in unstimulated peripheral blood T-cells, peripheral blood cells, and EBV-transformed B-cell line, or a T-cell leukemia line. WO 00/20593. IL-17 is expressed in arthritic, but not normal joints (reviewed in Martel-Pelletier, J. *et al.*, *Front. Biosci.* 4: d694-703 (1999). While expression of IL-17 is restricted, the IL-17 receptor is widely expressed, a property consistent with the pleiotropic activities of IL-17. IL-17 stimulates epithelial, endothelial, and fibroblastic cells to secrete cytokines such as IL-6, IL-8, and granulocyte-colony-stimulating factor (G-CSF), as well as prostaglandin $E_2$ ($PGE_2$). Spriggs, M.K., *supra.*; Broxmeyer, H.E., *supra.* IL-17 can sustain proliferation and preferential maturation of CD34- hemopoietic progenitors into neutrophils when cultured with fibroblasts. As such, production of IL-17 may be the key mechanism by which T-cells regulate the hematopoietic system. See, Yao, *et al.*, *J. Immunol.*, 155(12): 5483-5486 (1995) [Yao-2], Fossiez, *et al.*, *J. Exp. Med.*, 183(6): 2593-2603 (1996); Kennedy, *et al.*, *J. Interferon Cytokine Res.*, 16(8): 611-617 (1996).

a1

Please replace the paragraph at page 16, lines 21-27 with the paragraph rewritten as follows:

IGF-1 has been proposed for the treatment or prevention of osteoarthritis. In fact, intra-articular administration of IGF-1 in combination with sodium pentosan polysulfate (a chondrocyte catabolic activity inhibitor) caused improved histological appearance, and near-normal levels of degradative enzymes (neutral metalloproteinases and collagenase), tissue inhibitors of metalloproteinase and matrix collagen. R.A. Rogachefsky, *et al.*, *Ann. N.Y. Acad. Sci.* 732: 392-394 (1994). The use of IGF-1 either alone or as an adjuvant with other growth factors to stimulate cartilage regeneration has been described in WO 91/19510, WO 92/13565, US 5,444,047, EP 434,652.

a2

Please replace the paragraph at page 17, lines 11-24 with the paragraph rewritten as follows:

Cartilage matrix degradation is believed to be due to cleavage of matrix molecules (proteoglycans and collagens) by proteases (reviewed in Woessner JF Jr., "Proteases of the extracellular matrix", in Mow, V., Ratcliffe, A. (eds): Structure and Function of Articular Cartilage. Boca Raton, FL, CRC Press, 1994 and Smith R.L., *Front. In Biosci.* 4:d704-712 (1999). While the key enzymes involved in matrix breakdown have not yet been clearly

a3

identified, matrix metalloproteinases (MMPs) and "aggrecanases" appear to play key roles in joint destruction. In addition, members of the serine and cysteine family of proteinases, for example the cathepsins and urokinase or tissue plasminogen activator (uPA and tPA) may also be involved. Plasmin, urokinase plasminogen activator (uPA) and tissue plasminogen activator (tPA) may play an important role in the activation pathway of the metalloproteinases. Evidence connects the closely related group of cathepsin B, L and S to matrix breakdown, and these cathepsins are somewhat increased in OA. Many cytokines, including IL-1, TNF-a and LIF induce MMP expression in chondrocytes. Induction of MMPs can be antagonized by TGF-β and is potentiated, at least in rabbits, by FGF and PDGF. As shown by animal studies, inhibitors of these proteases (MMPs and aggrecanases) may at least partially protect joint tissue from damage *in vivo*.

Please replace the paragraph at page 19, lines 28-33 with the paragraph rewritten as follows:

The pathology of OA involves not only the degeneration of articular cartilage leading to eburnation of bone, but also extensive remodelling of subchondral bone resulting in the so-called sclerosis of this tissue. These bony changes are often accompanied by the formation of subchondral cysts as a result of focal resorption. Agents which inhibit bone resorption, *i.e.*, osteoprotegerin or bisphosphonates have shown promising results in animal models of arthritis, and therefore show promise in treating cartilagenous disorders. Kong *et al.*, *Nature* 402: 304-308 (1999).

Please replace the paragraph at page 32, lines 6-15 with the paragraph rewritten as follows:

B. Mouse Patellae Assay

This experiment examines the effects of the test compound on proteoglycan synthesis in the patellae (knee caps) of mice. This assay uses intact cartilage (including the underlying bone) and thus tests factors under conditions which approximate the *in vivo* environment of cartilage. Compounds are either added to patellae *in vitro*, or are injected into knee joints *in vivo* prior to analysis of proteoglycan synthesis in patellae *ex vivo*. As has been shown previously, *in vivo* treated patellae show distinct changes in PG synthesis *ex vivo*. (Van den Berg *et al.*, *Rheum. Int.* 1: 165-9 (1982); Verschure, P.J. *et al.*, *Ann. Rheum. Dis.* 53: 455-460 (1994); and Van de Loo *et*

a5 word

*al.*, *Arthrit. Rheum.* 38: 164-172 (1995). In this model, the contralateral joint of each animal can be used as a control. The procedure is described in greater detail in the examples.

Please replace the paragraph beginning at page 32, lines 30 and ending at page 33, line 6 with the paragraph rewritten as follows:

D. Aggrecanase assay

Aggrecan is the major proteoglycan of cartilage and largely responsible for the mechanical properties of articular cartilage. Arner *et al.*, *J. Biol. Chem.* 274(10):6594-6601 (1999). Aggrecan contains two N-terminal globular domain, G1 and G2, separated by a proteolytically sensitive interglobular domain (IGD), followed by a glycosaminoglycan (GAG) attachment region and a C-terminal globular domain (G3). The G1 domain of aggrecan interacts with hyaluronic acid and link protein to form large aggregates containing multiple aggrecan monomers that are trapped within the cartilage matrix. Hardingham, T.E. & Muir, H., *Biochim. Biophys. Acta* 279: 401-405 (1972); Heinegard, D. & Hascall, V.C., *J. Biol. Chem.* 249: 4250-4256 (1974); Hardingham, T.E., *Biochem. J.* 177: 237-247 (1979). Aggrecan provides normal cartilage with its properties of compressibility and resilience, and is one of the first matrix components to undergo measurable loss in arthritis. This loss appears to be due to an increased rate of aggrecan degradation that can be attributed to proteolytic cleaveage within the IGD of the core protein. Cleavage within this region generates large C-terminal, GAG-containing aggrecan fragments lacking the $G_1$ domain which are unable to bind to hyaluronic acid and thus diffuse out of the cartilage matrix.

a6

Please replace the paragraph at page 33, lines 7-14 with the paragraph rewritten as follows:

Cleavage of aggrecan has been shown to occur at $Asn^{341}$-$Phe^{342}$ and at $Glu^{373}$-$Ala^{374}$ within the interglobular domain. Matrix mellaoproteinases (MMP-1, -2, -3, -7, -8, -9 and -13) are known to cleave aggrecan *in vitro* at the $Asn^{341}$-$Phe^{342}$ site. Fosang *et al.*, *J. Biol. Chem.* 266: 15579-15582 (1991); Flannery, C.R. *et al.*, *J. Biol. Chem.* 267: 1008-1014 (1992); Fosang *et al.*, *Biochem. J.* 295: 273-276 (1993); Fosang *et al.*, *J. Biol. Chem.* 267: 19470-19474 (1992); Fosang *et al.*, FEBS Lett. 380: 17-20 (1996). Identification of G1 fragments formed by cleavage at the $Asn^{341}$-$Phe^{342}$ site within human articular cartilage as well as in synovial fluids suggests a

a7

a7. cont.

role for MMPs in proteoglycan degredation *in vivo*. Arner *et al.*, *supra*. However, these MMPs were not responsible for the cleavage at the $Glu^{373}$-$Ala^{374}$ site.

Please replace the paragraph at page 63, lines 8-17 with the paragraph rewritten as follows:

**Example 1A**

**Effect of IL-17 upon cartilage matrix metabolism**

a8

To determine whether IL-17 affects cartilage matrix metabolism, porcine articular cartilage explants were treated with a range of IL-17 concentrations, and proteoglycan synthesis and breakdown were measured. At concentrations as low as 0.1 ng/ml, IL-17 induced significant cartilage breakdown (Fig. 1A) and inhibited new matrix synthesis (Figure 1B), with comparable potency to IL-1α. When IL-1α (1 ng/ml) and IL-17 (0.1 or 1 ng/ml) were combined, an enhancing, apparently additive, effect was observed on both matrix breakdown (Fig. 1C) and synthesis (Fig. 1D). Unlike what was found in a prior study (Chabaud *et al.*, Arthritis Rheum. 42(5): 963-970 (1999), no synergism between IL-1α and IL-17 was observed.

Please replace the paragraph at page 67, lines 1-12 with the paragraph rewritten as follows:

**Example 3**

***In vivo* effects of IL-17**

a9

The patellar assay determines the *in vitro* and *in vivo* effect of the tested compound on proteoglycan synthesis in the patellae of mice. The patella is a very useful model to study the effects of the test compound because it permits the evaluation on cartilage which has not been removed from the underlying bone. Moreover, since each animal has one patellae in each leg, experiments can be performed using the contralateral joint as a control. This assay involves injection of a protein into the intra-articular space of a (mouse) knee joint, and subsequent harvest (within a few days after injection) of the patella (knee cap) for measurement of matrix synthesis. The procedure performed herein, has been previously used to measure effects of cytokines *in vitro* and *in vivo* (Van den Berg *et al.*, *Rheum. Int.* 1: 165-9 (1982); Verschure P.J. *et al.*, *Ann. Rheum. Dis.* 53: 455-460 (1994); and Van de Loo *et al.*, *Arthrit. Rheum.* 38: 164-172 (1995)).

Please replace the paragraph at page 70, lines 11-25 with the paragraph rewritten as follows:

Soluble factors made by T cells, monocytes and synovial fibroblasts may act in concert as these cell types are found in close proximity in RA synovium. The fact that IL-17 induces expression of other cytokines, such as TNF-α and IL-1α Chabaud *et al.*, *J. Immunol.* 161: 409-414, (1998); Jovanovic *et al.*, *J. Immunol.* 160: 3513-21 (1998), which are found at high levels in diseased joints, Arend and Dayer, *Arthritis Rheum.* 38: 151-60 (1995), raises the intriguing possibility that IL-17 is involved in the initiation of the inflammatory cascade in arthritis. Overproduction of IL-17 by human mononuclear cells is triggered by IL-1β and IL-15 (Ziolkowska *et al.*, *supra*), and IL-17 is likely responsible for production of IL-6 (Chaubaud *et al.*, *supra*) and LIF, Chabaud *et al. J. Immunol.* 161: 409-414 (1998) and induction of bone resorption (Kotake *et al.*, *J. Clin. Invest.* 103: 1345-1351 (1999) by RA synovial tissues. Thus, IL-17 may be one of the primary catabolic cytokines in arthritis. IL-17 may also perpetuate the cycle of cytokine synthesis as overproduction of IL-17 by human mononuclear cells is triggered by IL-1β and IL-15 (Ziolkowska *et al.*, *supra*). As described herein, IL-17 disrupted cartilage matrix homeostasis and augmented the detrimental effects of IL-1α on articular cartilage matrix turnover and nitric oxide production. Thus, the presence of IL-17 in a diseased joint can amplify the inflammatory cascade and exacerbate skeletal tissue breakdown in human joints.

a10

Please replace the paragraph at page 78, lines 21-33 with the paragraph rewritten as follows:

a11

Articular cartilage explants: The metacarpophalangeal joint of a 4-6 month old female pigs was aseptically dissected, and articular cartilage is removed by free-hand slicing in a careful manner so as to avoid the underlying bone. The cartilage was minced and cultured in bulk for at least 24 hours in a humidified atmosphere of 95% air 5% $CO_2$ in serum free (SF) media (DMEM/F12, 1:1) with 0.1% BSA and antibiotics. After washing three times, approximately 80 mg of articular cartilage was aliquoted into micronics tubes and incubated for at least 24 hours in the above SF media. Test proteins were then added at 1% either alone or in combination with IL-1α (10 ng/ml). Media was harvested and changed at various timepoints (0, 24, 48, 72 hours) and assayed for proteoglycan content using the 1,9-dimethyl-methylene blue (DMB) colorimetric assay described in Farndale and Buttle, *Biochem. Biophys. Acta* 883: 173-177 (1986). After labeling (overnight) with $^{35}$S-sulfur, the tubes were weighed to determine the amount of tissue. Following an overnight digestion, the amount of proteoglycan remaining in the tissue as well as proteolgycan synthesis ($^{35}$S-incorporation) was determined.